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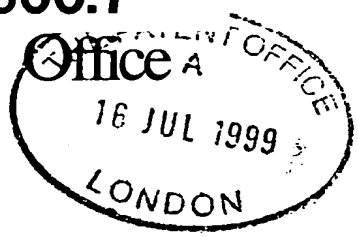

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1. Your reference — N.77399 - NP/MPR/mrm

2. Patent application number
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — POWDERJECT RESEARCH LTD, 4 Robert Robinson Avenue, The Oxford Science Park, Oxford OX4 4GA.

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom 07511071001.

4. Title of the invention — NEEDLELESS SYRINGE

5. Name of your agent *(if you have one)* — J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — 14 SOUTH SQUARE
GRAY'S INN
LONDON WC1R 5LX

Patents ADP number *(if you know it)* — 16002. 26001

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Claim(s)	5
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature J. A. Kemp & Co. Date 16 July 1999

12. Name and daytime telephone number of person to contact in the United Kingdom: ROBERTS, Mark Peter 0171 405 3292

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DUPLICATE

NEEDLELESS SYRINGE

The present invention relates generally to a needleless syringe device for accelerating particles for delivery into target tissue of a vertebrate subject.

The ability to deliver pharmaceuticals through skin surfaces (transdermal delivery) provides many advantages over oral or parenteral delivery techniques. In particular, transdermal delivery provides a safe, convenient and noninvasive alternative to traditional drug administration systems, conveniently avoiding the major problems associated with oral delivery (e.g. variable rates of absorption and metabolism, gastrointestinal irritation and/or bitter or unpleasant drug tastes) or parenteral delivery (e.g. needle pain, the risk of introducing infection to treated individuals, the risk of contamination or infection of health care workers caused by accidental needle-sticks and the disposal of used needles). In addition, transdermal delivery affords a high degree of control over blood concentrations of administered pharmaceuticals.

Recently, a novel transdermal drug delivery system that entails the use of a needleless syringe to fire powders (i.e. solid drug-containing particles) in controlled doses into and through intact skin has been described. In particular, US Patent No. 5,630,796 to Bellhouse et al. describes a needleless syringe that delivers pharmaceutical particles entrained in a supersonic gas flow. The needleless syringe can be used for transdermal delivery of powdered therapeutic compounds and compositions (e.g. drugs, vaccines, etc.), for delivery of genetic material into living cells (e.g. gene therapy) and for the delivery of biopharmaceuticals to skin, muscle, blood or lymph. The needleless syringe can also be used in conjunction with surgery to deliver particles to organ surfaces, solid tumors and/or to surgical cavities (e.g. tumor beds or cavities after tumor resection). In theory, practically any pharmaceutical agent that can be prepared in a substantially solid, particulate form can be safely and easily delivered using such devices.

One needleless syringe described in Bellhouse et al. comprises an elongate tubular over-expanded converging-diverging nozzle having a rupturable membrane initially closing the passage through the nozzle and arranged substantially adjacent to the upstream end of the nozzle. Particles to be delivered are disposed adjacent to the

rupturable membrane and are delivered using an energizing means which applies gaseous pressure to the upstream side of the membrane sufficient to rupture the membrane and produce a supersonic gas flow (containing the pharmaceutical particles) through the nozzle for delivery from the downstream end thereof.

Transdermal delivery using the needleless syringe described in Bellhouse et al. is carried out with particles having an approximate size that generally ranges from between 0.1 and 250 μm. For drug delivery, an optimal particle size is usually at least about 10 to 15 μm (the size of a typical cell). For gene delivery, an optimal particle size is generally substantially smaller than 10 μm. Particles larger than about 250 μm can also be delivered from the device, with the upper limitation being the point at which the size of the particles would cause untoward damage to the skin cells. The actual distance which the delivered particles will penetrate depends upon particle size (e.g. the nominal particle diameter assuming a roughly spherical particle geometry), particle density, the initial velocity at which the particle impacts the skin surface, and the density and kinematic viscosity of the skin. In this regard, optimal particle densities for use in needleless injection generally range between about 0.1 and 25 g/cm^3, preferably between about 0.8 and 1.5 g/cm^3, and injection velocities generally range between about 100 and 3000 m/sec. These particle size and density ranges are also appropriate to the present invention.

There are two distinct phases of gas flow that occur in the device. The first phase is associated with the shock waves produced upon rupturing of the membrane and is called "the starting process" (or "starting transient"). The second regime of flow occurs upstream of the shock and expansion waves associated with starting process and is called quasi-steady nozzle flow.

As discussed in Bellhouse et al, it was considered that the particle velocity depended upon the flow in the starting process. The starting process is generated by a sudden impulse change in pressure within the divergent nozzle, and in the Bellhouse et al device is initiated at the throat of the nozzle. This is shown by the space-time (x-t) diagram of Figure 1. This Figure shows the distance downstream (positive values of x) and upstream (negative values of x) of the nozzle exit plane (i.e. the distal end of the nozzle) along the abscissa and shows time on the ordinate. The time starts when the

device is actuated. After rupturing of the membrane, a steep front of high pressure (a shock wave 11) sweeps downstream along the length of the nozzle. This is closely followed by the so-called "contact surface" 12.

The contact surface 12 is the boundary between the gases that were previously separated by the membrane. It is well acknowledged that the gases do not mix appreciably at this boundary so the effect is one of the driver gas (the gas upstream of the membrane before rupturing) "pushing" the driven gas (the gas downstream of the membrane before rupturing) out of the nozzle like a piston, with the contact surface being analogous to the face of the piston. The contact surface 12 is closely followed by a secondary shock wave 13. The secondary shock wave 13 is followed by a series of oblique shock fronts 16 within a starting process (region 1 in Figure 1) with large variations in gas density and velocity (and therefore particle velocity).

The starting process is followed by a regime of quasi-steady flow (in region 3). The quasi-steady flow is clean, that is to say substantially free of shock and expansion waves such that the velocity at a given point changes slowly enough with time to be accurately modelled by steady flow non time-varying equations. Quasi-steady flow is thus different from truly steady flow in which the Mach number at a given point does not change over time, and unsteady flow in which the Mach number at a given point varies, and the flow is governed by unsteady equations. Both the starting process and quasi-steady flow are terminated by an oblique shock front 15 that is swept upstream of the nozzle exit, as a result of over-expanded nozzle operation. As is mentioned in Bellhouse et al, it was thought that the particles, being initially positioned on, or very near to, the rupturable membrane, travelled with the contact surface 12 between the fronts of the primary and secondary shock waves 11,13. In the light of investigations by the present inventors, this view is now believed to be over-simplistic and (as is discussed later) the gas-particle flow in prior art devices is more complicated with groups of particles being accelerated by different mechanisms. It is still true that the starting process is critical to the acceleration of a proportion of the particles in prior art devices. In contrast to this, the essence of the present invention is based on the idea of trying to avoid entraining the particles in the starting process.

Previous devices have utilised over-expanded nozzles which have an exit cross-

sectional area A_e greater than the exit cross-sectional area of a correctly-expanded noz $A_{correct}$. Over-expanded operation occurs when the ratio P_{tot}/P_e of the total pressure P_{tot} to the ambient exit pressure P_e is inadequate for a given nozzle area ratio A_1/A_e (where A_1 is the minimum diameter in the system). An overexpanded nozzle was used in prior art devices because, in order to obtain an adequate spread of payload on the target, it was thought that a large exit area was required. However, experiments conducted by the present inventors have shown that using an over-expanded nozzle leads to flow non-uniformities such as oblique (or normal) stationary shock waves in the flow which serve to detach the flow from the nozzle walls. This flow accelerates the particles in a separated jet. Thus, surprisingly, it has been found that using a larger exit area does not necessarily increase the useful target area and in fact often causes the flow to detach resulting in a central jet core forming and a consequent low payload spread.

Furthermore, devices of the prior art (such as those described in Bellhouse et al) utilise a convergent nozzle portion downstream of the particle-containing cassette. This portion acts as the interface between the relatively large membrane diameter and the relatively small nozzle throat diameter. The chosen throat diameter is controlled by the desired maximum choked mass flow rate through the device and the chosen membrane diameter is controlled by the need to be easily able to manufacture the cassette and hold the dose of particles required. Thus, upon actuation, the particles are forced through a constriction in the device. It is thought that this may increase both particle-wall attrition and particle-particle attrition, both of which mechanisms reduce the particle size and thereby undesirably affect the acceleration and penetration characteristics of the particles.

Experimental research sponsored by the present applicant has shown that the prior art devices produce two distinctive types of particle behaviour. Results from time resolved DGV (Doppler Global Velocimetry) measurements are shown in Figure 2. This shows a cross-section of the divergent portion of a nozzle 20 and gives the instantaneous speed of the particles at a time of 177 μs after rupture of the membrane (not shown).

As can be seen, the leading particles 21 are delivered in a wide cloud at a typical velocity of 200 - 400 m/s. A narrower quasi-steady stream of particles 22 follows the

leading cloud at 650 - 800 m/s (please note the white circular image centred on the plane of the nozzle exit together with the dark shadow on its right hand boundary as drawn is an artefact produced by this measurement technique). The leading particles are associated with the transient starting process in the gas flow, while the high speed particles are entrained in the quasi-steady nozzle flow. As has been mentioned, the nozzle in this prior art device is over-expanded which means oblique shocks will be present in the nozzle. The detachment of the high velocity particle stream from the nozzle walls is a direct consequence of the shock induced separation of the nozzle gas flow due to these shocks. Referring again to Figure 1, the gas flow has been broadly categorised into three flow regimes:

i) The Starting Process (region 1)

ii) Shock-Processed Flow (region 2)

iii) Quasi-Steady Supersonic Flow (region 3)

The particle trajectories 17 are also shown in Figure 1. As can be seen, a significant proportion of the particles are accelerated within the starting process but then decelerate as they reach the secondary shock wave 13 and contact surface 12. A cloud front 18 of particles is seen to decelerate as it leaves the nozzle, the nozzle exit being represented by x=0 These particles are those entrained with the initial 200 - 400 m/s cloud attached to the nozzle wall. By nature, the starting process creates a flow having large variations in axial gas velocity and density. These are thought to be the two most important parameters for particle acceleration. There are also large variations in gas velocity and density radially. This flow regime is therefore considered unsuitable for drug delivery if uniform velocities and distributions are required. Another fraction of particles do not reach the secondary shock 13 but are processed firstly by the oblique shocks 16 within the starting process (in region 1) and then the upstream moving oblique shock 15 which defines the separated flow within region 2. The final component of the particle payload is accelerated within the quasi-steady flow (region 3, particle trajectories not shown in Figure), before being separated by the quasi-stationary shock front 14 (defined in region 2). This acceleration path leads to the highest particle velocity of 850 m/s confined to a separated jet of approximately 9 mm diameter.

It seems, contrary to previous beliefs, that the starting process, rather than being

the chief accelerator of the particles, actually acts as an impediment to high velo particles. The particles which exit initially in a large cloud seem to act as a barrier to particles entrained in the subsequent quasi-steady flow resulting in lower overall particle velocities, which can be undesirable.

The present invention arises from the idea that, if one can prevent the particles from being entrained in the starting process flow, then all of the particles will be entrained in the subsequent quasi-steady supersonic flow, resulting in higher and more uniform particle velocities. The present invention also alleviates the problem of jetting by using a substantially correctly expanded nozzle and particle attrition by dispensing with a convergence downstream of the membrane.

Accordingly, the present invention includes a needleless injection device comprising:

a driver chamber arranged, in use, to contain a charge of pressurised gas;

a duct section connected to said driver chamber to receive gas therefrom;

closure means for preventing the flow of gas from said driver chamber to said duct section until said closure means is opened; and

a dose of particles positioned within the device in the region of said closure means;

said device being so constructed and arranged that upon opening of said closure means, a shock wave is produced to travel along said duct section in a downstream direction and a substantially quasi-steady gas flow is established in said duct section upstream of said shock wave, said particles being substantially wholly entrained in said substantially quasi-steady flow to be accelerated thereby and expelled from the device.

The present invention also includes a method of accelerating a dose of particles in a needleless injection device having a driver chamber and a duct section downstream of said driver chamber, the method comprising:

opening closure means located between said driver chamber and said duct section;

producing a shock wave travelling in a downstream direction in said duct section;

establishing a substantially quasi-steady flow of fluid in said duct section upstream of said shock wave; and

entraining substantially all the particles in said substantially quasi-steady flow.

Preferably, the shock wave initiates a starting process upon reaching the downstream end of the duct section.

The driver chamber may be pre-charged with gas or could be connected to a source of gas operable to charge the driver chamber with pressurised gas. The driver chamber may be constituted by a constant area tube or may have a convergence at its downstream end.

The duct section is advantageously of a constant cross-sectional area and the particles are usefully positioned upstream of the closure means.

Preferably, there is no convergent portion downstream of the closure means and there is a divergent portion downstream of the duct section. The divergent portion preferably has an area ratio such that flow there through is substantially correctly expanded and may also be contoured to prevent reflected oblique shock waves forming in the divergence and/or to provide a uniform distribution of particles.

A further closure means may be provided and this and/or the first said closure means may comprise a rupturable membrane. When two closure means are used, the particles are advantageously positioned between them and the upstream closure may have a lower opening pressure than the downstream closure.

A further aspect of the invention provides a particle retention assembly of or for use in a needleless injection device; said assembly comprising:

first closure means arranged to open when the pressure across it is P_1; and

second closure means which, in use, is located upstream of said first closure means and which is arranged to open when the pressure across it is P_2;

wherein $P_1 > P_2$.

In connection with this aspect, there is also provided a method of entraining a dose of particles in a gas flow in a needleless injection device, the method comprising:

opening an upstream closure means when the pressure difference there across is P_1 to produce a cloud of particles;

entraining said particles in said cloud of gas; and

opening a downstream closure area when the downstream closure area is expo to said cloud of gas and entrained particles are when the pressure difference across said downstream closure means is P_2;

wherein $P_1<P_2$.

Preferably, particles are positioned between the first and second closure means.

Embodiments of needleless syringe device in accordance with the present invention will now be described, by way of example only, with reference to the accompanying drawings in which:

Figure 1 shows schematically an *x-t* diagram which describes the flow regimes present in a prior art device similar to the ones described in Bellhouse et al;

Figure 2 shows a cross-sectional view of the nozzle and the instantaneous axial velocity of particles exiting the above-mentioned prior art device after 177μs of flow;

Figure 3 shows schematically an *x-t* diagram which describes the flow regimes present in a device according to an embodiment of the present invention;

Figure 4 shows a schematic cross-sectional side elevation of a target surface and an impingement region;

Figure 5 shows a needleless injection device according to an embodiment of the invention in schematic cross-sectional side elevation;

Figure 6 shows a part of a schematic *x-t* diagram which describes the behaviour of the starting process in a device according to the present invention when the gas in region 2 is subsonic;

Figures 7a and 7b are schematic cross-sectional (before and after) side elevations of the membrane region of a duct section of a further embodiment of a needleless injection device and illustrate a further aspect of the invention wherein the duct section has an enlarged duct portion to keep a more constant cross sectional area after membrane bursting;

Figure 8 shows a modification to the Figure 5 embodiment wherein the driver chamber has a larger cross-sectional area than the duct section, only part of the device being shown;

Figures 9a, 9b and 9c are a sequence of schematic cross-sectional side elevations

of the membrane region of yet a further embodiment of a needleless injection device and show another aspect of the invention relating to the creation of a mixed gas-particle cloud between two closures in a driver chamber.

The first embodiment of the invention is an air powered, disposable device and is shown schematically in Figure 5. The device could, however, be reusable and/or powered by a fluid other than air, for example helium.

The device comprises an elongate tubular driver chamber 51 attached to a cylindrical duct section (or shock tube) 52 of the same diameter as the driver chamber 51. In this embodiment, each tube has a 6mm diameter, but in general the diameters can be different to one another and can be of any practical size.

In this embodiment, the driver chamber 51 has a length of 65 mm and the duct section 52 has a length of 30 mm. Other lengths are possible, and in fact the determination of the lengths is important in influencing the performance of the device (see later).

At the interface between the driver chamber 51 and duct section 52 is a rupturable membrane 53. The membrane 53 is of the type disclosed in Bellhouse et al and typically ruptures at around 20 bar pressure difference across it. The rupture pressure is an important device parameter but other rupture pressures could also be used depending on the desired results.

The downstream end of the duct section 52 is provided with a conical divergent nozzle 54 in this embodiment. The nozzle 54 has an area ratio A_e/A_t such that correctly expanded flow is established within it when the membrane 53 has ruptured and the driver chamber 51 discharges. In practice this ratio (A_e/A_t) could range from 1 to 50. The nozzle 54 has a 6° half-angle (ie a 12° cone angle) which is not so steep as to cause flow separation. Half angles up to 25° could be used in practice. The divergent nozzle 54 could take other forms and, in fact, is not essential to the present invention.

The driver chamber 51 is connected at its upstream end to a reservoir 55 of pressurised gas (in this case air) by a small diameter bleed hole 56. Other gases which are sterile and easily obtainable such as helium, nitrogen, argon or CO_2 are also suitable.

The gas pressure in the reservoir 55 should be sufficient for the gas to be able to

pass into the driver chamber 51 and rupture the membrane 53. In this embodiment the gas pressure is 60 bar but could be higher or lower depending on the membrane rupturing pressure. Also, other energising means (such as explosive charges) could be used to discharge gas into the driver chamber 51.

The reservoir 55 may be connected to the bleed hole 56 in a standard way (such as with a valve 57 as shown in the Figure) such that a flow of gas from the reservoir 55 to the driver chamber 51 can be initiated on demand. In this embodiment the bleed hole 56 has a diameter of 0.4 mm. This effectively de-couples the reservoir 55 and driver chamber 51 during the period of device operation (for an explanation of de-coupling, see below). However, other sizes of bleed hole could be used (for e.g. from 0.1 mm to 5 mm). When larger holes are used, total decoupling would not be established and the total pressure P_{tot} in the driver chamber 51 would be able to rise as the device is actuated (with de-coupling, the total pressure remains constant).

As a further alternative, the driver chamber 51 could be pre-charged with pressurised gas and the reservoir 55 omitted. In such an arrangement, the membrane 53 could be punctured mechanically to actuate the device.

The particles 58 to be accelerated are in this embodiment initially located in the driver chamber 51 in the region of the rupturable membrane 53. The particles 58 do not necessarily have to be located adjacent to the membrane 53 initially. If they are located anywhere in the driver chamber 51 initially, they will not be entrained in the starting transient and so the invention should still operate. Also, the particles 58 could be located adjacent to the downstream side of the membrane 53 and the device should still work.

The functioning of this device is shown schematically by the x-t diagram in Figure 3, x=0 corresponding to membrane rupture. When the reservoir valve 57 is opened, gas flows from the reservoir 55 to the driver chamber 51 via the bleed hole 56 until the membrane rupture pressure is reached in the driver chamber 51. Thus, upon rupturing of the membrane 53, a shock 31 is generated which travels down the duct section 52 in the downstream direction. After a characteristic shock formation distance, the shock 31 travels ahead of the contact surface 32 at a constant speed. The contact surface 32 follows closely behind the shock 31 and the particles 33 follow behind that.

Three flow regions can be identified:

i) Quiescent gas ahead of the shock wave 31 (region 1)

ii) Gas between the shock 31 and the contact surface 32 (region 2)

iii) Gas between the contact surface 32 and the particles 33 (region 3)

The distance between the particles 33 and the contact surface 32 increases with time. This is a result of the constant area duct section 52. The function of the duct section 52 is therefore seen to be one of "buying time"; it increases the separation between the shock 31 (which will initiate the starting process at the transition between the duct 52 and the divergent nozzle 54) and the particles 33. The instantaneous delay time t_D (the time between the starting process initiating and the particles reaching the divergence 54) is a function of the particle size and gas type, whereby larger and denser particles are delayed more.

Simultaneously to the above, a first *(u-a)* expansion wave 34 moves at a constant velocity (initially the speed of sound in the gas, a) from the location of the ruptured membrane 53 in the upstream direction until it reaches the bleed hole 56. Here it is reflected back as a *(u+a)* wave 36 in the downstream direction where it accelerates until it eventually exits through the nozzle 54. The gas velocity in the downstream direction is denoted by u and the local speed of sound in the gas is denoted by a.

As the shock 31 moves through the tube in region 2, it serves to process the quiescent gas in region 1 to be in region 2 and heats the gas in region 1 up, increasing its temperature and reducing its density. This is the so-called "shock-heating" process.

When the shock 31 reaches the start of the divergent nozzle 54, the starting process is initiated and a second *(u-a)* wave 35 is produced at the transition between the constant area 52 and divergence 54. This wave 35 travels relatively slowly along the nozzle 54 in the downstream direction and accelerates once the contact surface 32 has overtaken it. This occurs because the gas ahead of the contact surface 32 in region 2 has been shock-heated by the passing of the shockwave and so has a different density to the gas behind the contact surface 32 in region 3. There is therefore a density discontinuity across the contact surface 32 meaning that the local speed of sound a is different in region 2 to the local speed of sound in region 3. In fact, the local speed of sound is higher in region 2 than region 3 due to the shock heating process that occurred in region

2. Thus, when the second *(u-a)* wave 35 gets overtaken by the contact surface 32 speeds up considerably in the downstream direction because the value of a drops suddenly (whereas the value of u is matched across the contact surface 32, u being the gas velocity). The shock heating process is therefore beneficial in containing the starting process and it assists in accelerating the starting process out of the device.

The length L_1 of the duct section 52 is chosen so that the bulk of the particle cloud 33 never catches up with the second *(u-a)* wave and so is substantially fully entrained in clean quasi-steady flow. This can be achieved by ensuring that the second *(u-a)* wave is not overtaken by the contact surface 32 and is thereby confined to region 2. Alternatively (and as shown in Figure 3), the second *(u-a)* wave 35 may pass into region 3 ahead of the particles 33. In other words, the device is arranged so that the final delay time t_f (the time between the second *(u-a)* wave 35 and the particles 33) is positive.

Further, the length L_1 of the duct section 52 is also important for the reason that, the longer it is, the more the particles 33 are accelerated (the gas in region 3 has a uniform density and velocity so the particles 33 experience a uniform acceleration). A long length would theoretically lead to particle velocities close to the gas velocity. However, in practice, increasing the length L_1 to beyond a certain point will give diminishing returns due to shock attenuation and the contact surface 32 moving closer to the shock wave 31 due to mixing caused by the boundary layer growth. There is therefore an optimum duct section length of L_1 which also depends on the other parameters (such as the driver gas species and pressure) of the system.

The length L_D of the driver chamber 51 is chosen so that the particles 58 have passed out of the device before the reflected expansion wave 36 passes out of the device. In other words, the length is preferably chosen so that the reflected expansion wave 36 cannot overtake the particle cloud 33. This length ideally needs to be longer if light gases are used in the driver chamber (e.g. helium) which have a higher speed of sound. Thus, the boundary in time between the point where the second *(u-a)* wave 35 passes (terminating the starting process) and the point where the reflected first *(u-a)* wave 36 passes delimit a regime of clean flow. Substantially all of the particles 58 are entrained in this regime of clean flow.

Upon actuation, the bleed hole 56 causes the driver chamber 51 to be filled

gradually until the membrane rupture pressure is reached. The bleed hole 56 (which could be constituted by an orifice plate) serves to ensure that during the discharge process, a negligible amount of gas is able to escape from the reservoir 55 into the driver chamber 51. The bleed hole 56 therefore effectively creates an end wall condition and has the effect of de-coupling the reservoir 55 from the flow system. Thus, the static pressure P_{static} in the driver chamber 51, remains substantially constant throughout the time the particles are accelerated. In this embodiment, the static pressure P_{static} in the driver chamber 51, is the membrane rupture pressure. The atmospheric exit pressure initially at the nozzle exit is denoted by P_e. The ratio P_3/P_e (P_3 is the static pressure in region 3) is matched via analytical equations to the ratio A_t/A_e to ensure correctly expanded flow through the nozzle section 54. Since the total pressure is constant, the nozzle 54 will be correctly expanded for substantially the whole operation of the device resulting in attached flow for substantially the whole actuation period. The flow is therefore clean and attached for the period whilst particles 58 are entrained. Experiments have shown that substantially clean and attached flow can also be obtained with an under expanded nozzle or even a slightly overexpanded nozzle.

Ensuring that the particles 58 are entrained in the quasi-steady flow is believed to provide a further advantage. When a flow impinges on a flat area 41 (in this case the skin or other tissue), an "impingement region" (see Figure 4) is set up. This region comprises a stagnation bubble 42 which serves to reduce the speed of the particles 58 as they approach the surface of the skin 41. It is believed that the contact surface 32 (which delimits a discontinuity in density) serves to "flatten" the impingement region making it thinner. Thus, particles 58 that reach the skin 41 after the contact surface 32 would undergo less deceleration in the flattened impingement region than those which arrive in the vicinity of the contact surface in prior art devices.

In the above embodiment, the gas flow in both regions 2 and 3 is supersonic (i.e. it has a Mach number, $M>1$). However it is to be noted that the device also works when the gas in region 2 has a Mach number of less than 1. In this case, the second *(u-a)* wave 35 initially travels upstream (because u is now smaller than a) as shown in Figure 6. However, when the second *(u-a)* wave reaches the contact surface 32, most of it reflects as a *(u+a)* wave 37 moving in the downstream direction, the rest being

transmitted into the cooler gas in region 3 as a weak *(u-a)* wave 38. As the cont surface 32 is passed, the local speed of sound *a* suddenly decreases which causes the *(u-a)* wave to accelerate in the downstream direction and out of the device.

If a driver gas other than air is used, for example helium, it is possible for the flow in region 3 to have a Mach number less than 1 while the flow in region 2 has a Mach number greater than 1. Experiments have shown such a device works because the *(u-a)* wave does not reach the contact surface, or if it does only a weak wave is transmitted into the flow.

It has been found that the device is quite sensitive to the membrane opening area. Thus, it is desirable that the membrane 53 when ruptured (or any other suitable closure when opened) should present an area substantially identical to the area of the duct section 52. An example of apparatus to achieve this is shown in Figures 7a and 7b . Figure 7a shows the situation before rupture. An annular channel 71 is disposed adjacent to the downstream side of the membrane 53 so that when the membrane 53 ruptures, the area presented to the gas flow is substantially constant (see Figure 7b). If the area presented is smaller, a constriction occurs in the flow resulting in undesirable gas dynamics such as the creation of a steady expansion and flow perturbations.

Although in the description above reference has been made to a single rupturable membrane, any other suitable closure could be used such as a membrane cassette or a non-membrane cassette.

The nozzle could be a simple divergent nozzle or one that is contoured using the method of characteristics modified for boundary layer corrections. This ensures that the steady state two dimensional *(u-a)* waves which occur at the transition between the constant duct section and the divergent portion are not reflected out of the nozzle.

It is thought that the invention will still operate satisfactorily if the divergent nozzle 54 is dispensed with completely. In such a case, the gas undergoes a rapid expansion at the downstream end of the duct section 52. This case is equivalent to under-expanded nozzle operation with a starting process in the jet analogous to the above starting process. Thus, a starting process of sorts is created even in the absence of a divergent nozzle and the concept of the invention is still applicable to devices having no divergent nozzle.

In the above embodiment, the driver chamber 51 is shown as having the same area as the duct section 52. However, the driver chamber 51 could be constructed so as to have a larger area than the duct section 52. This is shown in Figure 8. Such a construction causes a weaker unsteady expansion fan and therefore a weaker *(u+a)* wave 36. The increased driver chamber area causes a weaker expansion wave which in turn is less likely to disrupt the acceleration of the particles 58. Further, this construction makes the device less sensitive to variations in the membrane opening area. It is to be noted that the driver chamber area A_0 is preferably not less than the duct section area A_1 because this would result effectively in a divergence at the membrane. This would create a *(u-a)* wave at the point where the particles start and so would be unlikely to allow the starting transient to pass out of the nozzle before the particles 58 are entrained in the gas flow.

Another aspect of the invention will now be described. Figure 9 shows a device having two membranes(91,92). The particles 58 are initially located between the two membranes in the driver chamber 51. The membranes are constituted so as to have different rupturing pressures, the upstream membrane 91 having a lower rupturing pressure than the downstream membrane 92. As the driver chamber 51 is filled and the upstream rupturing pressure is reached, the first membrane 91 ruptures, during which a jet of gas 93 discharges into the volume where the particles 58 are retained. This jet 93 causes mixing of the gas and particles to create a gas-particle cloud that is quite uniform. Thus, when the downstream membrane 92 ruptures at a higher pressure, the particles 58 are already entrained in a cloud and a more uniform spread of particles is obtained. The delay time caused by the difference in rupturing pressure of the two membranes is sufficient to allow gas-particle mixing and a cloud to form and thereby overcome the effect of gravity which causes the particles to bunch together at the lowest point in the device before rupture of the upstream membrane 92. Beneficially, a distance greater than one membrane diameter should separate the two membranes to allow for good mixing. As a further modification, the particles 58 could initially be located upstream of the upstream membrane 91. When the upstream membrane 91 ruptures, the gas flowing into the space between the membranes carries the particles 58 with it and mixing is thus effected to produce a cloud in the same way as described above.

CLAIMS

1. A needleless injection device comprising:

a driver chamber arranged, in use, to contain a charge of pressurised gas;

a duct section connected to said driver chamber to receive gas therefrom;

closure means for preventing the flow of gas from said driver chamber to said duct section until said closure means is opened; and

a dose of particles positioned within the device in the region of said closure means;

said device being so constructed and arranged that upon opening of said closure means, a shock wave is produced to travel along said duct section in a downstream direction and a substantially quasi-steady gas flow is established in said duct section upstream of said shock wave, said particles being substantially wholly entrained in said substantially quasi-steady flow to be accelerated thereby and expelled from the device.

2. A needleless injection device according to claim 1, wherein said shock wave initiates a starting process upon reaching the downstream end of the duct section.

3 A needleless injection device according to claim 1 or 2, wherein said driver chamber is pre-charged with pressurised gas.

4. A needleless injection device according to claim 1 or 2, further comprising a source of gaseous fluid, said driver chamber being fluidly connected to said source and arranged to be provided with said charge of pressurised gas by said source upon opening of the fluid connection therebetween.

5. A needleless injection device according to claim 4, wherein said fluid connection is comprised by a bleed hole.

6. A needleless injection device according to any one of the preceding claims,

wherein said duct section comprises a tube of substantially constant cross-sectional area.

7. A needleless injection device according to any one of the preceding claims, in which said particles are positioned upstream of said closure means.

8. A needleless injection device according to any one of the preceding claims, wherein said duct section has substantially no convergent portion downstream of said closure means.

9. A needleless injection device according to any one of the preceding claims, further comprising a divergent portion positioned downstream of said duct section.

10. A needleless injection device according to claim 9, wherein said divergent portion has an inlet cross-sectional area and an exit cross-sectional area, said areas being chosen in accordance with the total driver chamber pressure at which said device is arranged to operate so that, in use, the gas flow in said divergent portion is substantially correctly expanded when said particles pass through said divergent portion.

11. A needleless injection device according to claim 9 or 10, wherein said divergent portion has an internal contour such that substantially no reflected oblique shock waves are formed in said substantially quasi-steady flow.

12. A needleless injection device according to claim 9, 10 or 11, wherein said divergent portion is contoured such as to cause any expansion downstream of the duct section to provide a generally uniform radial distribution of particles exiting the device.

13. A needleless injection device according to any one of the preceding claims, wherein said driver chamber comprises a substantially constant area tube.

14. A needleless injection device according to any one of the preceding claims, wherein said driver chamber comprises a convergence at its downstream end.

15. A needleless injection device according to any one of the preceding claims, wherein said closure means comprises a rupturable membrane arranged to open by rupturing.

16. A needleless injection device according to any one of the preceding claims, wherein said gaseous fluid is air.

17. A needleless injection device according to any one of the preceding claims, wherein said device contains a further closure means.

18. A needleless injection device according to claim 17, wherein said further closure means is positioned in said driver chamber upstream of said particles.

19. A needleless injection device according to claim 17 or 18, wherein said further closure means comprises a rupturable membrane arranged to open by rupturing.

20. A needleless injection device according to claim 17, 18 or 19 wherein the said closure means is arranged to open when the pressure across it is P_1, said further closure means is arranged to open when the pressure across it is P_2 and $P_1 > P_2$.

21. A particle retention assembly of or for use in a needleless injection device; said assembly comprising:

first closure means arranged to open when the pressure across it is P_1; and

second closure means which, in use, is located upstream of said first closure means and which is arranged to open when the pressure across it is P_2;

wherein $P_1 > P_2$.

22. An assembly according to claim 21 further comprising a dose of particles located between said first and second closure means.

23. An assembly as claimed in claim 21 or 22, wherein the assembly is of, or for use in, a needleless injection device having the construction claimed in any of claims 1 to 20.

24. A needleless injection device comprising the assembly of any one of claims 21 to 23.

25. A method of accelerating a dose of particles in a needleless injection device having a driver chamber and a duct section downstream of said driver chamber, the method comprising:

opening closure means located between said driver chamber and said duct section;

producing a shock wave travelling in a downstream direction in said duct section;

establishing a substantially quasi-steady flow of fluid in said duct section upstream of said shock wave; and

entraining substantially all the particles in said substantially quasi-steady flow.

26. A method of accelerating a dose of particles in a needleless injection device according to claim 25, further comprising initiating a starting process when said shock wave reaches the downstream end of said duct section.

27. A method of accelerating particles according to claim 25 or 26, wherein said entrained particles are accelerated along a duct section of substantially constant area.

28. A method of accelerating particles according to claim 25, 26 or 27 wherein said particles are initially positioned upstream of said closure means.

29. A method of accelerating particles according to any one of claims 25 to 28 wherein said particles do not pass through a constriction downstream of said closure

means.

30. A method of accelerating particles according to any one of claims 25 to 29 further comprising passing said quasi-steady flow of fluid through a divergent nozzle positioned downstream of said duct section.

31. A method of accelerating particles according to any one of claims 25 to 30 further comprising opening a further closure means before opening the first said closure.

32. A method of needleless injection involving the injection of particles into bodily tissue, the method comprising accelerating the particles in a needleless injection device using the method of acceleration claimed in any one of claims 25 to 31.

33. A method of entraining a dose of particles in a gas flow in a needleless injection device, the method comprising:

opening an upstream closure means when the pressure difference there across is P_1 to produce a cloud of gas;

entraining said particles in said cloud of gas; and

opening a downstream closure area when the downstream closure area is exposed to said cloud of gas and entrained particles are when the pressure difference across said downstream closure means is P_2;

wherein $P_1<P_2$.

34. A method of needleless injection involving the injection of particles into bodily tissue, the method comprising entraining the particles in a gas flow in a needleless injection device using the method of particle entrainment claimed in claim 33.

ABSTRACT

NEEDLELESS SYRINGE

Experiments have shown that a proportion of the particles delivered by a prior art needleless syringe are influenced by the so-called novel "starting process". However, there are certain disadvantages associated with accelerating particles in a starting process and the present invention suggests a solution to the problem by providing a device and method which ensures that most of the particles are entrained in the steady flow which follows behind the starting process. A particle retaining assembly and method is also disclosed.

FIG. 1

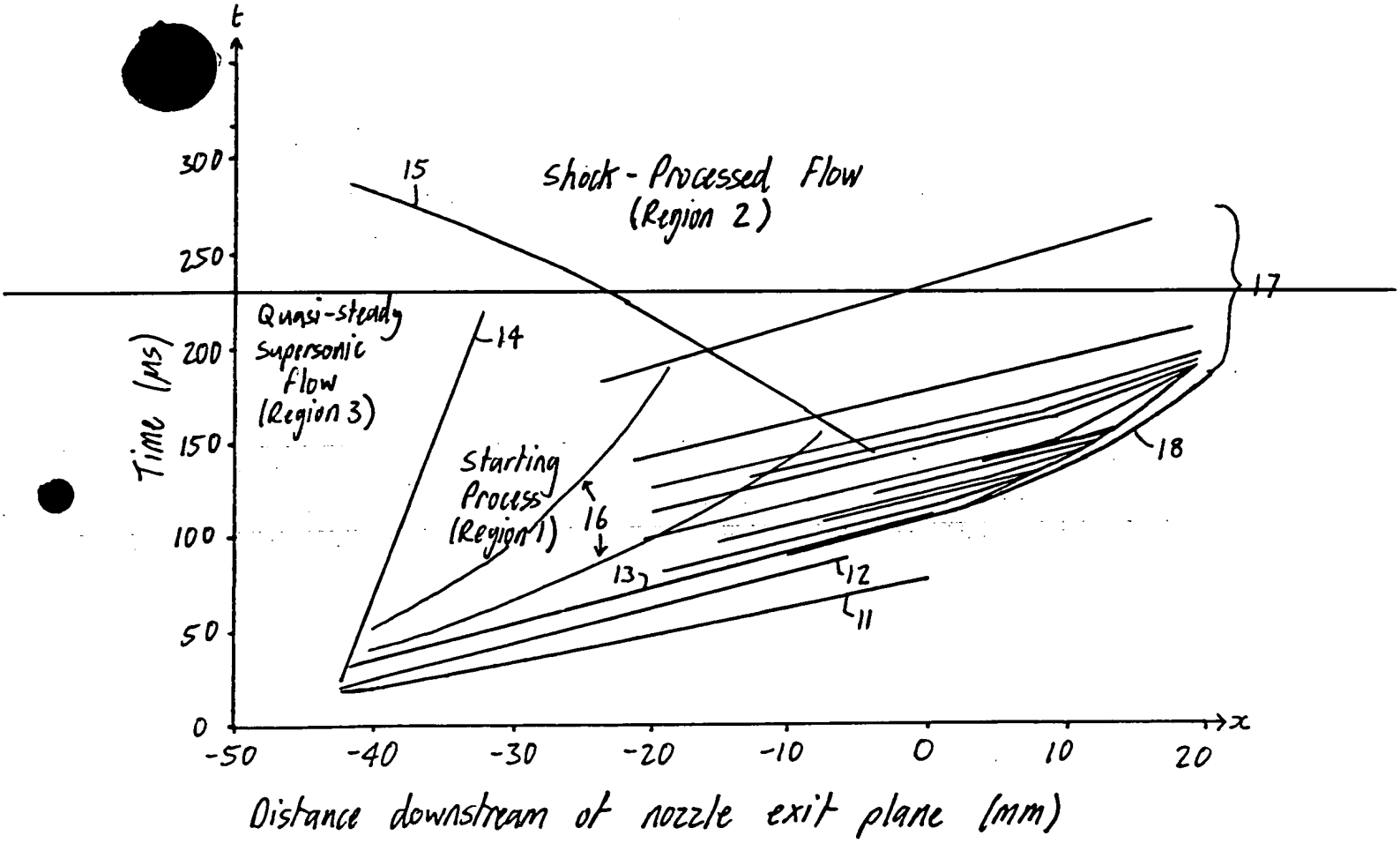
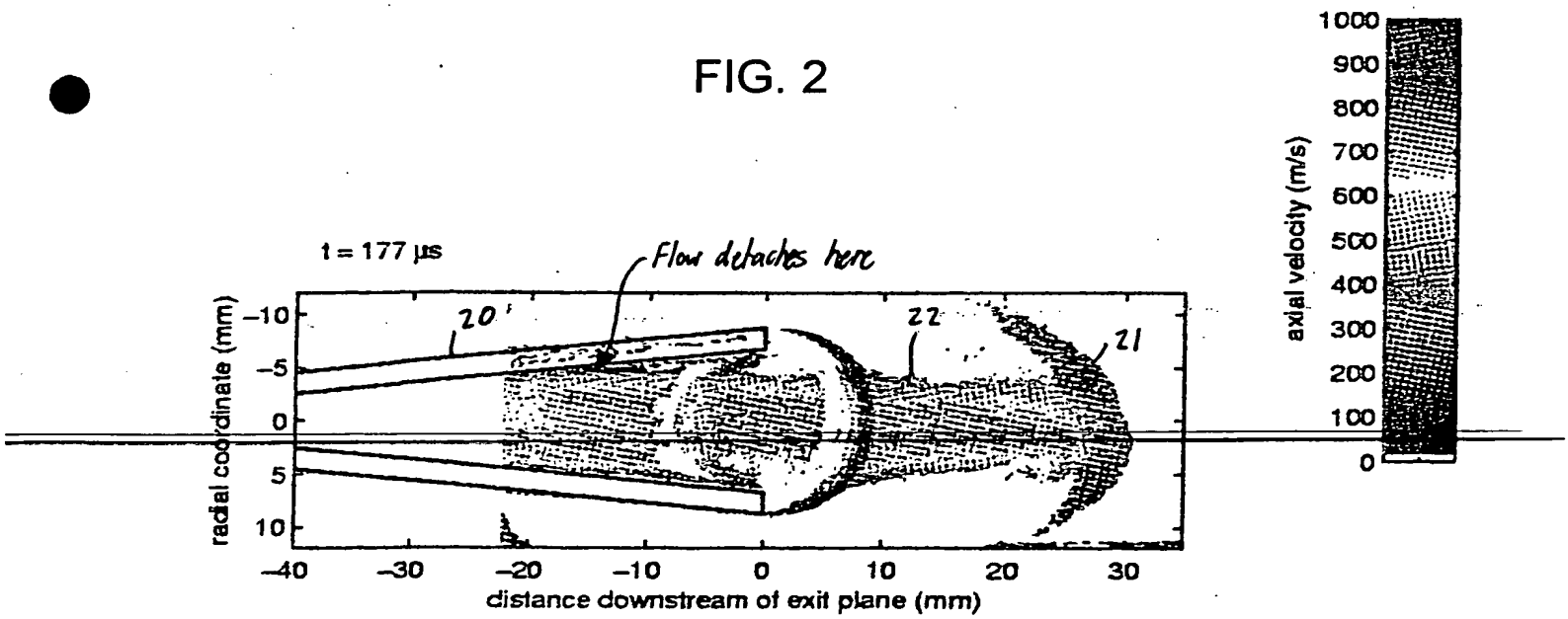

t
300
250
200
150
100
50
0
Time (μs)
15
Shock-Processed Flow
(Region 2)
17
Quasi-steady
supersonic
flow
(Region 3)
14
Starting
Process
(Region 1)
16
18
13
12
11
-50
-40
-30
-20
-10
0
10
20
x
Distance downstream of nozzle exit plane (mm)

FIG. 2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Flow detaches here
20
22
21
radial coordinate (mm)
-10
-5
0
5
10
-40
-30
-20
-10
0
10
20
30
distance downstream of exit plane (mm)
axial velocity (m/s)
1000
900
800
700
600
500
400
300
200
100
0

FIG. 3

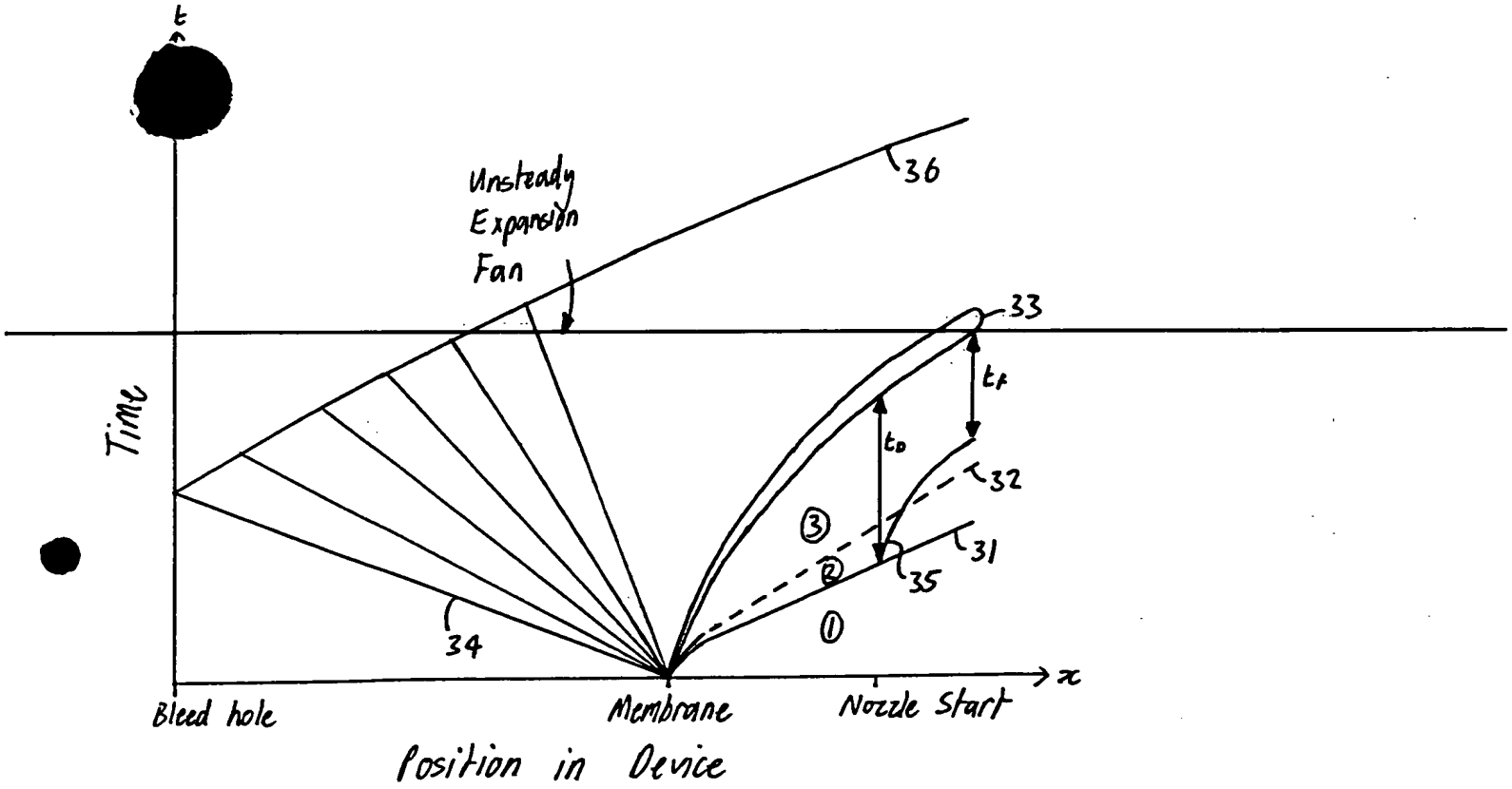

t
Unsteady
Expansion
Fan
36
33
Time
t_f
t_D
32
3
2
31
35
1
34
x
Bleed hole
Membrane
Nozzle Start
Position in Device

FIG. 4

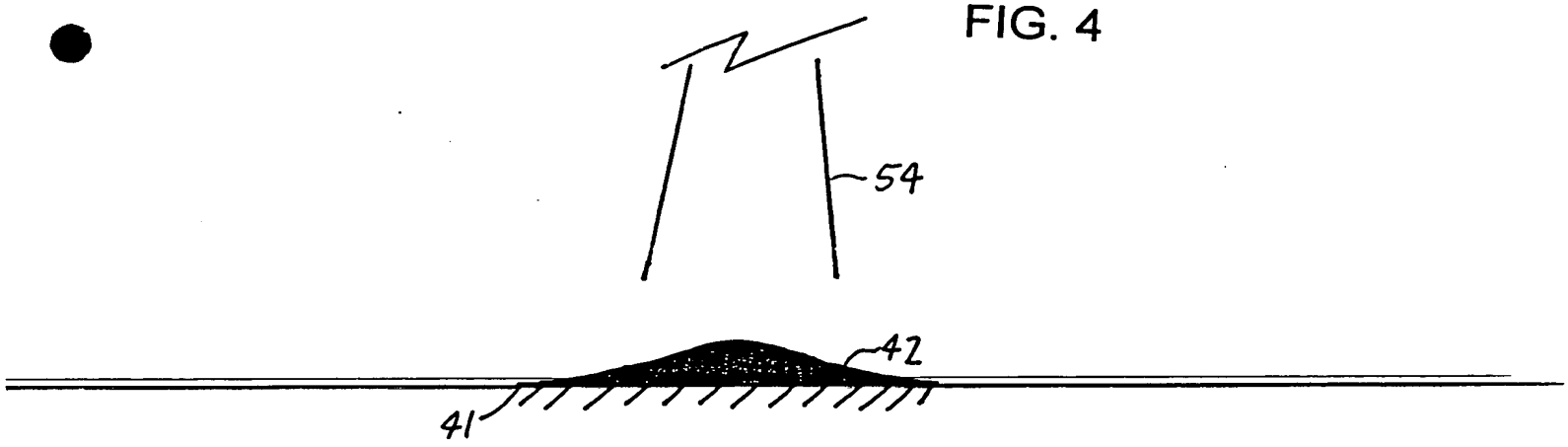

54
42
41

FIG. 5

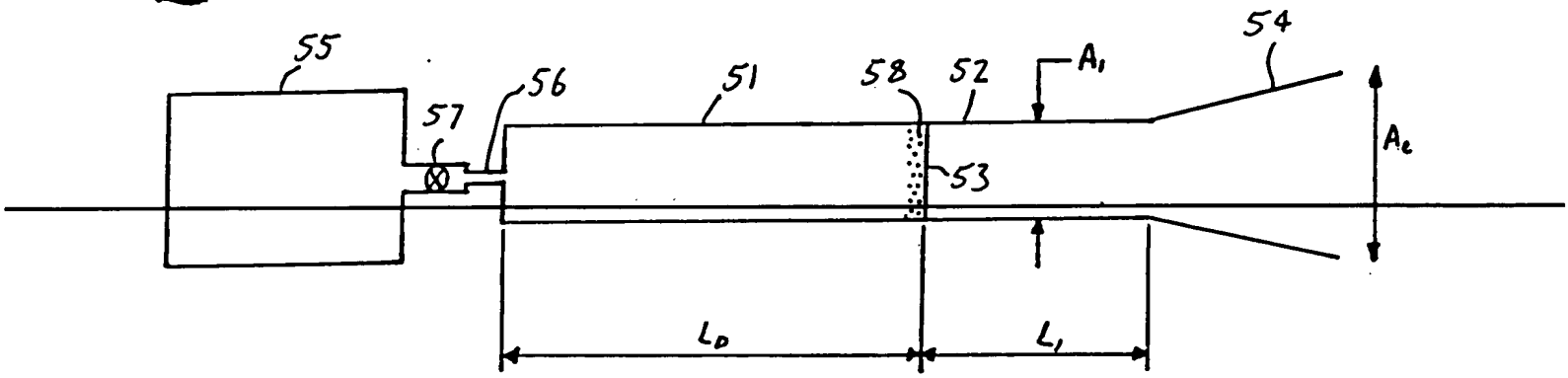


FIG. 6

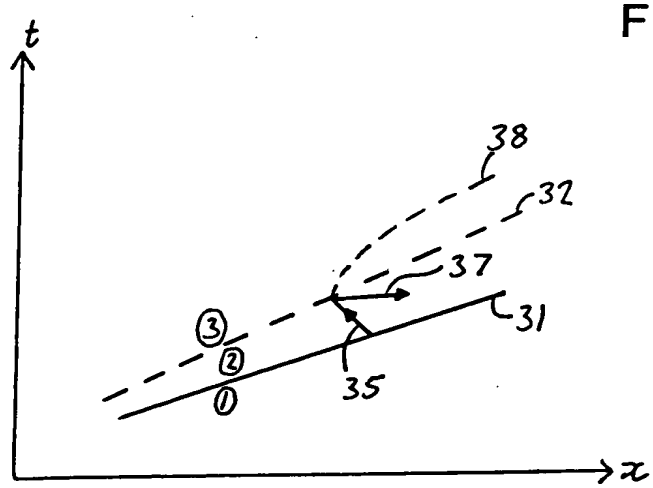


FIG. 7a

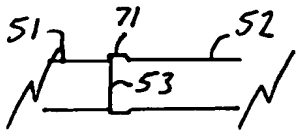


FIG. 7b

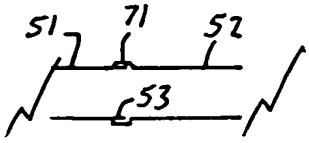
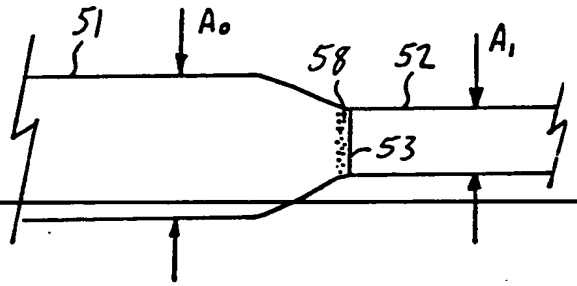


FIG. 8



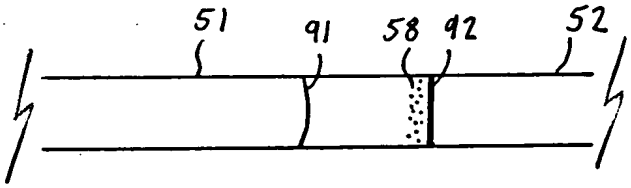


FIG. 9a

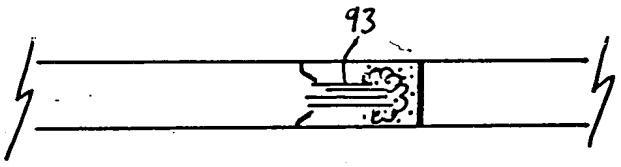


FIG. 9b

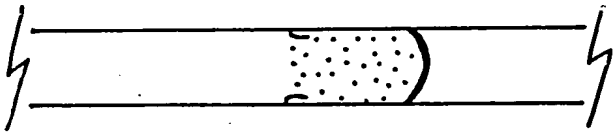


FIG. 9c

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